

## **REMARKS**

The Office Action mailed August 26, 2002, has been received and its contents carefully noted. The pending claims, claims 10, and 12-26, were rejected. By this amendment, claims 10, 12-23, and 25-26 have been amended and claim 24 has been cancelled. Support may be found in the specification and claims as originally filed. No statutory new matter has been added. Reconsideration is respectfully requested.

### **Rejection Under 35 U.S.C. § 112**

The Examiner rejected claims under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner deemed that the claims are incomplete for omitting essential steps and that it is not clear how the incorporation of 13-HODE into formulations of omega-3 fatty acids is enabling of "correcting the inhibition of endogenous 13-HODE synthesis by omega-3 fatty acids."

Applicants respectfully submit that the claims as amended obviate the rejection. Specifically, claim 10 as amended is directed to a method of prevention the inhibition of endogenous 13-HODE synthesis which may occur by the oral administration of an omega-3 fatty acid which comprises orally administering to a subject an omega-3 fatty acid formulation comprising 13-HODE. Therefore, the rejection under 35 U.S.C. 112, second paragraph, should properly be withdrawn.

### **Prior Art Rejections**

Prior to responding to the specific prior art rejections, Applicants respectfully submit that prior to the present invention, therapies employing 13-HODE administration encountered various problems. In particular, 13-HODE is relatively unstable and easily metabolized. Thus, oral administration of prior art compositions comprising 13-HODE was discouraged as the 13-HODE was readily metabolized thereby decreasing the expected therapeutic benefits of 13-HODE therapy. The present invention solves the problems encountered with oral administration of 13-HODE by orally administering 13-HODE in an omega-3 fatty acid formulation. Since endogenous 13-HODE synthesis is inhibited by the oral administration of long chain omega-3 fatty acids, the inventors surprisingly discovered that the oral formulation comprising 13-HODE

and omega-3 fatty acids were not readily metabolized and therefore exhibited greater therapeutic benefits and that the omega-3 fatty acids did not further inhibit endogenous 13-HODE synthesis. Example 1 shows when 13-HODE is administered in the form of a solution in the ethyl ester of EPA endogenous 13-HODE synthesis in the vascular endothelium is not inhibited and actually raises the levels of 13-HODE.

#### **Rejection Under 35 U.S.C. § 102(a)**

The Examiner rejected claims 14-15, 18-20 and 23 under 35 U.S.C. §102(a) as being anticipated by Carlsson et al. (WO 99/44585). Specifically, the Examiner deemed that although the composition of Carlsson et al. differs from the claimed composition in that the claimed composition is for oral use, the Examiner stated that such intended use or purpose is not limited to the interpretation of the composition claim and therefore the reference clearly anticipates the claimed invention.

Applicants respectfully submit that Carlsson et al. exclusively relates to topical applications. Nowhere do Carlsson et al. raise or address the problems of oral formulations of 13-HODE. Most importantly, nowhere do Carlsson et al. discuss or address the issue of providing 13-HODE and omega-3 fatty acids in the same formulation. Therefore, the disclosure of Carlsson et al. does not anticipate each and every limitation of the invention as claimed and the rejection under 35 U.S.C. 102(a) should properly be withdrawn.

#### **Rejection Under 35 U.S.C. § 103(a)**

The Examiner rejected claims 10, 12-13 and 24-26 under 35 U.S.C. §103(a) as being unpatentable over Miller et al. (J Invest Dermatol, 1990, 94:353-358). Specifically, the Examiner deemed that one having ordinary skill in the art would have known that the administration of 13-HODE could reverse the suppression of endogenous 13-HODE synthesis induced by n-3 PUFA such as EPA and DHA, one having ordinary skill in the art would have expected that the coadministration of 13-HODE with omega-3 fatty acid (e.g., EPA and DHA) could correct the inhibition of endogenous 13-HODE with omega-3 fatty acid, and one having ordinary skill in the art would have been motivated to modify the teaching of Miller et al. such that the side effect induced by omega-3 fatty acid would be greatly reduced. The Examiner also deemed that one having ordinary skill in the art would have been motivated to select the claimed compound such as ethyl-EPA and ethyl-DHA with the expectation that ethyl ester of EPA and

ethyl ester of DHA would not significantly alter the analogous properties of compound of the reference due to a close structural similarity of the compounds.

Applicants respectfully submit that one of ordinary skill in the art would not be motivated to coadminister 13-HODE with omega-3 fatty acids in order to prevent the endogenous 13-HODE synthesis with a reasonable expectation of success. Specifically, as explained above, it is known that omega-3 fatty acids inhibit endogenous 13-HODE synthesis when orally administered. Thus, one of ordinary skill in the art would not reasonably expect that oral administration of 13-HODE in combination with omega-3 fatty acids would prevent inhibition of endogenous 13-HODE synthesis and actually increase 13-HODE levels. Nowhere does the Examiner provide logical reasoning as to why one of ordinary skill in the art would combine 13-HODE with omega-3 fatty acids when oral administration of omega-3 fatty acids have been found to inhibit endogenous 13-HODE synthesis.]

Additionally, Miller et al. only relates to topical administration of 13-HODE and does not relate to oral administration of 13-HODE. As discussed above, with topical administration, none of the issues that relate to oral administration are relevant. The topical formulation is directly applied to and incorporated in the tissue. Thus, one of ordinary skill in the art would not use the teachings and disclosure of Miller et al. to modify the topical formulation to obtain an oral formulation which addresses the problems of orally administering 13-HODE and omega-3 fatty acids. Therefore, the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

The Examiner rejected claims 16-17 and 21-22 under 25 U.S.C. 103(a) as being unpatentable over Streber (US 5102912) in view of Carlsson et al. (WO 99/44585). Specifically, the Examiner deemed that one having ordinary skill in the art would have been motivated to incorporate phospholipids (lecithin) in a 13-HODE composition, with the reasonable expectation of success, such that the pharmacological profile would be enhanced.

Applicants respectfully submits that the Examiner over-simplifies the problems of administering fatty acids and does not appreciate the many specific differences there are between each specific type of phospholipids, fatty acid or other lipids. Each specific lipid has its own specific properties which depend on its precise chemical composition and which are not necessarily possessed by other specific lipids. Applicants submit that Streber relates to diseases produced by oestrogen and to other situations. Streber does describe oral formulations but of 9-HODE and not 13-HODE which is a quite different substance with quite different properties.

Nowhere does Steber teach or suggest the combination of omega-3 fatty acids and 13-HODE to address the problem of 13-HODE synthesis suppression which may occur with orally administered omega-3 fatty acids.

Applicants respectfully submit that a prima facie case of obviousness has not been established. Specifically, the combination of Carlsson et al. and Streber does not result in the invention as claimed. In particular, the combination of Carlsson et al. and Streber does not result in an oral composition comprising both 13-HODE and at least one omega-3 fatty acid. Therefore, the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

The Examiner rejected claim 24 under 35 U.S.C. 103(a) as being unpatentable over Carlsson et al. (WO 99/44585). Specifically, the Examiner deemed that the selection of suitable oil, for example canola oil, among various oily materials described in Carlsson to prepare various 13-HODE formulation is well considered within the skill of the artisan, that one having ordinary skill in the art would have known that canola oil is a natural source of omega-3 fatty acid, and since the present claims do not specifically state that omega-3 fatty acid must essentially be used in the isolated form, the claimed invention is rendered obvious.

Applicants respectfully submit that the claims as amended require both 13-HODE and an omega-3 fatty acid. As explained above, nowhere do Carlsson et al. disclose or suggest formulations comprising both 13-HODE and at least one omega-3 fatty acid. Therefore, claim 24 as amended is nonobvious and the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

#### **Request for Interview**

Applicants respectfully request either a telephonic or an in-person interview should there be any remaining issues.

#### **Extension of Time**

A Petition for an Extension of Time for one (1) month under 37 C.F.R. 1.136 and the appropriate fee are submitted herewith to extend the time for responding to the Office Action to December 26, 2002.

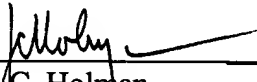
## Conclusion

Accordingly, in view of the foregoing amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of the claims to allow these claims and to find this application to be in allowable condition.

If the Examiner believes that a conference would be of value in expediting the prosecution of this application, the Examiner is invited to telephone the undersigned to arrange for such a conference.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

Respectfully submitted,  
JACOBSON HOLMAN PLLC

By   
John C. Holman  
Reg. No. 22,769

400 Seventh Street, N.W.  
Washington, D.C. 20004-2201  
(202) 638-6666  
Date: December 20, 2002  
Atty. Docket: 12660/P66570US0  
JCH/SKS

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

### In the claims:

Please amend claims 10, 12-23, and 25-26 as follows:

10. (Amended) A method of [correcting] preventing the inhibition of endogenous 13-HODE synthesis [by omega-3 fatty acids by incorporating 13-HODE into formulations of omega-3 fatty acids] which may occur when omega-3 fatty acids are orally administered to a subject which comprises orally administering to the subject an omega-3 fatty acid formulation comprising 13-HODE.

12. (Twice amended) The method of claim 10, wherein the omega-3 fatty acid formulation comprises [is selected from the group consisting of] EPA, DHA, a derivative of EPA, [and] a derivative of DHA, or a combination thereof.

13. (Twice amended) The method of claim 10, wherein the omega-3 fatty acid [is] formulation comprises ethyl-EPA, [or] ethyl-DHA, or both.

14. (Amended) [A] An oral pharmaceutical composition [for oral administration of] comprising 13-hydroxyoctadeca-9Z, 11E-dienoic acid (13-HODE) in its free form and at least one omega-3 fatty acid.

15. (Amended) [A] The oral pharmaceutical composition of claim 14 and further comprising [13-hydroxyoctadeca-9Z, 11E-dienoic acid (13-HODE) for oral administration, comprising, 13 HODE and] a pharmaceutically acceptable carrier.

16. (Twice amended) The oral pharmaceutical composition of claim 14 wherein the daily dose of 13-HODE is equal to or less than 100 mg.

17. (Amended) The oral pharmaceutical composition of claim 15, wherein the carrier is a mono-, di- or triglyceride oil.

18. (Amended) The oral pharmaceutical composition of claim 15, wherein the carrier is selected from the group consisting of corn, sunflower, safflower, cottonseed, grape seed, olive, evening primrose, borage, fish body, and fish liver oils.

19. (Amended) The oral pharmaceutical composition of claim 15, wherein the carrier is an ester of a fatty acid containing 16-26 carbon atoms and one or more double bonds.

20. (Amended) The oral pharmaceutical composition of claim 15, wherein the carrier is selected from the group consisting of ethyl-eicosapentaenoic (ethyl-EPA), oleic, linoleic, alpha-linolenic, stearidonic, gamma-linolenic, dihomogammalinolenic, arachidonic, docosapentaenoic and docosahexaenoic (ethyl-DHA).

21. (Twice amended) The oral pharmaceutical composition of claim 14 wherein the composition is administered in the form selected from the group consisting of tablets, dragees, capsules, granules, solutions, suspensions and lyophilized compositions.

22. (Twice amended) The oral pharmaceutical composition of claim 14 wherein the composition further comprises a fat-soluble antioxidant selected from the group consisting of ascorbyl palmitate, tocopherols, and ascorbic acid in the presence of lecithin.

23. (Twice amended) The oral pharmaceutical composition of claim 14 wherein the composition further comprises an additive selected from the group consisting of aggregants, disaggregants, osmotic pressure regulating salts, buffers, sweeteners, and coloring agents.

25. (Amended) The oral pharmaceutical composition of claim [24]14, wherein the omega-3 fatty acid is selected from the group consisting of EPA, DHA, a derivative of EPA, and a derivative of DHA.

26. (Amended) The oral pharmaceutical composition of claim [24]14, wherein the omega-3 fatty acid is selected from the group consisting of ethyl-EPA and ethyl-DHA.